REMARKS

The specification has been amended to provide sequence identification numbers for nucleotide and amino acid sequences within the specification. In addition, a new Sequence Listing is provided to conform the sequence identification numbers found in the specification with those of the Sequence Listing. No new matter has been added by these amendments.

A marked-up version of the amended paragraphs indicating the changes made and a clean version of these paragraphs reflecting entry of the amendments are enclosed.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 3 August 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Chiaki Senoo et al.	Art Unit:	
Serial No.:	09/831,180	Examiner:	
Filed:	May 3, 2001	Customer No.:	21559
Title:	NOVEL TRYPSIN FAMILY SERINE PROTEASES		

BOX PCT
Assistant Commissioner For Patents
Washington, D.C. 20231

STATEMENT UNDER 37 C.F.R. § 1.821-1.825

In reply to the Notification to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures mailed on June 7, 2001 and as required by 37 C.F.R. § 1.825(a), enclosed is an amended Sequence Listing consisting of 25 sheets to be inserted at the end of the application, replacing the current Sequence Listing.

In the accompanying Reply to Notification to Comply with Sequence Requirements, Applicants amend the application to comply with the requirements set forth in 37 C.F.R. § 1.821-1.825. As required by 37 C.F.R. § 1.821(d), sequence identifiers are now used throughout the application description and claims to refer to their respective sequences.

The enclosed Sequence Listing includes all nucleotide and amino acid sequences described in the application, as required by 37 C.F.R. § 1.821(c). Each sequence in the application appears separately in the Sequence Listing and each sequence in the Sequence Listing is assigned a separate sequence identifier. I hereby submit that the substitute sheets contain no new matter.

As required by 37 C.F.R. § 1.825(b), enclosed is a diskette containing a copy of the sequence listing in computer readable form including all previously submitted data with the amendments incorporated therein. The contents of the computer readable form are the same as the contents of the paper sheets.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 3 August 2001

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50026.027001 Sequence Statement under 1.825.wpd

Version with Markings to Show Changes Made

Replace the paragraph beginning on page 31, line 11, with the following paragraph.

--Figure 1 shows the mouse "Tespec PRO-1" cDNA sequence (SEQ ID NO:1) and the amino acid sequence thereof (SEQ ID NO:2). The active sites of trypsin-family serine proteases are indicated by underlines. The poly A signal is marked with a wavy line.--

Replace the paragraph beginning on page 31, line 15, with the following paragraph.

--Figure 2 shows mouse "Tespec PRO-2" cDNA sequence (SEQ ID NO:3) and the amino acid sequence thereof (SEQ ID NO:4). The active sites of trypsin-family serine protease are indicated by underlines. The poly A signal is marked with a wavy line.--

Replace the paragraph beginning on page 31, line 19, with the following paragraph.

--Figure 3 shows an alignment of amino acid sequences of mouse "Tespec PRO-1" (SEQ ID NO:2), "Tespec PRO-2" (SEQ ID NO:4), and known proteases (SEQ ID NOS:51-53). Amino acids conserved among all the proteins are marked with "*" and amino acids with similar characteristics are marked with ":". The active sites of trypsin-family serine protease are boxed.--

Replace the paragraph beginning on page 32, line 18, with the following paragraph.

--Figure 9 shows human "Tespec PRO-2" cDNA sequence (SEQ ID NO:5) and the amino acid sequence thereof (SEQ ID NO:6). The active sites of trypsin-family serine protease are indicated by underlines. The poly A signal is marked with a wavy line.--

Replace the paragraph beginning on page 32, line 22, with the following paragraph.

--Figure 10 shows a comparison of amino acid sequence between mouse (SEQ ID NO:3) and human (SEQ ID NO:5) "Tespec PRO-2". The nucleotides conserved between the two are boxed.--

Replace the paragraph beginning on page 32, line 25, with the following paragraph.

--Figure 11 shows a comparison of amino acid sequence between mouse (SEQ ID NO:4) and human (SEQ ID NO:6) "Tespec PRO-2". Amino acid residues shared between the two are indicated by "*" and amino acids with similar characteristics are indicated by ":". The active sites of trypsin-family serine protease are boxed.--

Replace the paragraph beginning on page 32, line 32, with the following paragraph.

--Figure 13 shows the nucleotide (SEQ ID NO:9) and amino acid (SEQ ID NO:10) sequences of human "Tespec PRO-3" cDNA. The active sites of trypsin-family serine protease are indicated by underlines. The poly A signal is marked with a wavy line.--

Replace the paragraph beginning on page 33, line 6, with the following paragraph.

--Figure 15 shows the mouse "Tespec PRO-3" cDNA sequence (SEQ ID NO:7) and the amino acid sequence thereof (SEQ ID NO:8). The active sites of trypsin-family serine proteases are indicated by underlines. The poly A signal is marked with a wavy line.--

Replace the paragraph beginning on page 33, line 10, with the following paragraph.

--Figure 16 shows a comparison of nucleotide sequence between mouse "Tespec PRO-3" (m. Tespec PRO-3) (SEQ ID NO:7) and human "Tespec PRO-3" (h. Tespec PRO-3) (SEQ ID NO:9). Nucleotides conserved between the two are boxed.--

Replace the paragraph beginning on page 33, line 13, with the following paragraph.

--Figure 17 shows a comparison of amino acid sequence between mouse "Tespec PRO-3" (m. Tespec PRO-3) (SEQ ID NO:8) and human "Tespec PRO-3" (h. Tespec PRO-3) (SEQ ID NO:10). Amino acid residues conserved between the two are boxed.--

Replace the paragraph beginning on page 38, line 13, with the following paragraph.

--"Tespec PRO-2" cDNA thus obtained consists of 1034 nucleotides (Figure 2) and its 5' non-coding region consists of 68 nucleotides. By contrast, the 3'-non-coding region of this cDNA is very shorter, consisting of only nine nucleotides. A putative poly A signal found in this cDNA is GATAAA, and it is predicted to be weaker signal as compared to the signal generally recognized in mRNAs (AAUAAA). Based on the sequence of this cDNA, "Tespec PRO-2" is predicted to encode 319 amino acids, which contains a possible region of signal peptide at its N-terminus. But, unlike "Tespec PRO-1", the protein does not contain a region rich in hydrophobic amino acids at its C-terminus. While the amino acid sequence contains a trypsin-family serine protease motif, "Trypsin-His", the "Trypsin-Ser" motif of this protein (GKCQGDSGAPMV) (SEQ ID NO:46) contains 2 amino acid residues that are deviated from the consensus sequence of the motif that consists of 12 amino acid residues ([DNSTAGC]-[GSTAPIMVQH]-X-X-G-[DE]-S-G-[GS]-[SAPHV]- [LIVMFYWH]-[LIVMFYSTANQH]) (SEQ ID NO:47). However, some known trypsin-family serine proteases have sequences that are different from the consensus sequence at several amino acid residues. "Tespec PRO-2" obtained is predicted to function as a protease.--

Replace the paragraph beginning on page 44, line 7, with the following paragraph.

--The human "Tespec PRO-2" cDNA consists of 1035 nucleotides and is predicted to encode 265 amino acids (Figure 9). Homology between human and mouse

"Tespec PRO-2" is 74.2% at the nucleotide level and 69.8% at the amino acid level. The amino acid sequence of the human "Tespec PRO-2" is shorter than that of mouse "Tespec PRO-2" by 54 residues at the C-terminus, and consequently, the human nucleotide sequence is longer in the 3'non-coding region as compared with that of the mouse gene (Figures 10 and 11). In addition, there is a region predicted to be a signal peptide at the N-terminus, and the C-terminal region is also rich in hydrophobic amino acids. The deduced amino acid sequence of human "Tespec PRO-2" contains a trypsin-family serine protease motif, "Trypsin-His". The motif of "Trypsin-Ser" of this protein contains an amino acid residue (GIFKGDSGAPLV) (SEQ ID NO:48) that is deviated from the consensus sequence in this motif that consists of 12 amino acid residues ([DNSTAGC]-[GSTAPIMVQH]-X-X-G-[DE]-S-G-[GS]-[SAPHV]- [LIVMFYWH]-[LIVMFYSTANQH]) (SEQ ID NO:47) (mouse "Tespec PRO-2" contains two amino acid residues deviated from the consensus sequence in this motif that consists of 12 amino acid residues).--

Replace the paragraph beginning on page 47, line 12, with the following paragraph.

--The mouse "Tespec PRO-3" cDNA consists of 1028 nucleotides and it is predicted to encode 321 amino acids (Figure 15). While the deduced amino acid sequence contains a "Trypsin-Ser" motif, it has the "Trypsin-His" motif that is deviated from the consensus motif consisting of 6 amino acids [LIVM]-[ST]-A-[STAG]-H-C (SEQ ID NO:49) at one amino acid residue (LTVAHC) (SEQ ID NO:50). However, like mouse "Tespec PRO-2", some known trypsin-family serine proteases have sequences

containing several amino acid deviation in the consensus sequence, and therefore mouse "Tespec PRO-3" is predicted to function as a protease. In addition, it has a hydrophobic region predicted to be a signal peptide at its N-terminus. Cysteine residues predicted to form an intramolecular disulfide bond are well conserved in the sequence relative to other serine proteases.--

Clean Versions of the Amended Paragraphs

Figure 1 shows the mouse "Tespec PRO-1" cDNA sequence (SEQ ID NO:1) and the amino acid sequence thereof (SEQ ID NO:2). The active sites of trypsin-family serine proteases are indicated by underlines. The poly A signal is marked with a wavy line.

Figure 2 shows mouse "Tespec PRO-2" cDNA sequence (SEQ ID NO:3) and the amino acid sequence thereof (SEQ ID NO:4). The active sites of trypsin-family serine protease are indicated by underlines. The poly A signal is marked with a wavy line.

Figure 3 shows an alignment of amino acid sequences of mouse "Tespec PRO-1" (SEQ ID NO:2), "Tespec PRO-2" (SEQ ID NO:4), and known proteases (SEQ ID NOS:51-53). Amino acids conserved among all the proteins are marked with "*" and amino acids with similar characteristics are marked with ":". The active sites of trypsin-family serine protease are boxed.

Figure 9 shows human "Tespec PRO-2" cDNA sequence (SEQ ID NO:5) and the amino acid sequence thereof (SEQ ID NO:6). The active sites of trypsin-family serine protease are indicated by underlines. The poly A signal is marked with a wavy line.

Figure 10 shows a comparison of amino acid sequence between mouse (SEQ ID NO:3) and human (SEQ ID NO:5) "Tespec PRO-2". The nucleotides conserved between the two are boxed.

Figure 11 shows a comparison of amino acid sequence between mouse (SEQ ID NO:4) and human (SEQ ID NO:6) "Tespec PRO-2". Amino acid residues shared between the two are indicated by "*" and amino acids with similar characteristics are indicated by ":". The active sites of trypsin-family serine protease are boxed.

Figure 13 shows the nucleotide (SEQ ID NO:9) and amino acid (SEQ ID NO:10) sequences of human "Tespec PRO-3" cDNA. The active sites of trypsin-family serine protease are indicated by underlines. The poly A signal is marked with a wavy line.

Figure 15 shows the mouse "Tespec PRO-3" cDNA sequence (SEQ ID NO:7) and the amino acid sequence thereof (SEQ ID NO:8). The active sites of trypsin-family serine proteases are indicated by underlines. The poly A signal is marked with a wavy line.

Figure 16 shows a comparison of nucleotide sequence between mouse "Tespec PRO-3" (m. Tespec PRO-3) (SEQ ID NO:7) and human "Tespec PRO-3" (h. Tespec PRO-3) (SEQ ID NO:9). Nucleotides conserved between the two are boxed.

Figure 17 shows a comparison of amino acid sequence between mouse "Tespec PRO-3" (m. Tespec PRO-3) (SEQ ID NO:8) and human "Tespec PRO-3" (h. Tespec PRO-3) (SEQ ID NO:10). Amino acid residues conserved between the two are boxed.

"Tespec PRO-2" cDNA thus obtained consists of 1034 nucleotides (Figure 2) and its 5' non-coding region consists of 68 nucleotides. By contrast, the 3'-non-coding region of this cDNA is very shorter, consisting of only nine nucleotides. A putative poly A signal found in this cDNA is GATAAA, and it is predicted to be weaker signal as compared to the signal generally recognized in mRNAs (AAUAAA). Based on the sequence of this cDNA, "Tespec PRO-2" is predicted to encode 319 amino acids, which contains a possible region of signal peptide at its N-terminus. But, unlike "Tespec PRO-1", the protein does not contain a region rich in hydrophobic amino acids at its C-terminus. While the amino acid sequence contains a trypsin-family serine protease motif, "Trypsin-His", the "Trypsin-Ser" motif of this protein (GKCQGDSGAPMV) (SEQ ID NO:46) contains 2 amino acid residues that are deviated from the consensus sequence of the motif that consists of 12 amino acid residues ([DNSTAGC]-[GSTAPIMVQH]-X-X-G-[DE]-S-G-[GS]-[SAPHV]- [LIVMFYWH]-[LIVMFYSTANQH]) (SEQ ID NO:47). However, some known trypsin-family serine proteases have sequences that are different from the consensus sequence at several amino acid residues. "Tespec PRO-2" obtained is predicted to function as a protease.

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The mouse "Tespec PRO-3" cDNA consists of 1028 nucleotides and it is predicted to encode 321 amino acids (Figure 15). While the deduced amino acid sequence contains a "Trypsin-Ser" motif, it has the "Trypsin-His" motif that is deviated from the consensus motif consisting of 6 amino acids [LIVM]-[ST]-A-[STAG]-H-C (SEQ ID NO:49) at one amino acid residue (LTVAHC) (SEQ ID NO:50). However, like mouse "Tespec PRO-2", some known trypsin-family serine proteases have sequences containing several amino acid deviation in the consensus sequence, and therefore mouse "Tespec PRO-3" is predicted to function as a protease. In addition, it has a hydrophobic

region predicted to be a signal peptide at its N-terminus. Cysteine residues predicted to form an intramolecular disulfide bond are well conserved in the sequence relative to other serine proteases.